Remarks

Claims 1-19, 21, and 24-33 are pending in the application. Claims 1-15 and 27 are withdrawn from consideration. Claims 20 and 22-23 are canceled. Claims of 16-19, 21, 24-26, and 28-33 are rejected.

Claim Amendments

Claim 16 is amended to clarify a method for producing optically induced mechanical forces on a target cell that is potentially cancerous. The clarification adds to the method the action of "directing a mechanical deformation of the target cell using the optical tweezer relative to the auxiliary object, a pushing force or a pulling force of the optical tweezer on the auxiliary object being transferred onto the target cell by the adhered auxiliary object as a one of said induced mechanical forces resulting in said deformation." Support for the amendment is found in the following passages and elsewhere in the description (reference numerals are omitted).

The "invention concerns a method to generate optically induced mechanical forces acting on elastic or deformable target objects by use of auxiliary objects" (page 1, lines 13-15). "The directed deformation of cells might be applied in investigations of diseases..." (page 1, lines 26-27). "When exerting a force on the erythrocytes, they are moved resulting in the deformation of the adhering target objects" (page 5, lines 12-14). "It is yet another object of the invention to provide a method to be able to deform/to stretch a target object to which an auxiliary object adheres by using two optical beams" (page 7, lines 29-32). "Due to a relative movement of the beams and/or a change in the focus the auxiliary object pulls/pushes the target object" (page 8, lines 2-4). "The change in the location of the focus relative to the erythrocyte can be adjusted by changing the position of the source of the laser light and/or of the

coverslip. Furthermore, the focus may possibly be altered by influencing optically within the area of the source of laser light" (page 13, lines 3-8). "Different cells... are pulled or pushed upon by the optical tweezer, the erythrocytes acting as force transducers" (page 9, lines 9-15). "The invention is derived from the optically induced forces within an optical tweezer to transfer forces onto elastic/deformable objects" (page 3, line 34-page 4, line 1). "This invention enables the deformation of adherent cells for several micrometers" (page 9, lines 29-30). Thus, changing a beam or a focus of the optical tweezer relative to the auxiliary object exerts a pushing or pulling force on the auxiliary object, which is transferred onto the target cell, resulting in a directed mechanical deformation of the target cell. Further actions and mechanisms regarding deformation of cells are discussed below with respect to added claims 34 and 35, and apply as support for the amendment to claim 16.

Claim 21 is amended to clarify limitations on a system for inducing optical forces for manipulating a target cell. The amendment adds "wherein a mechanical deformation of the target cell is directed using the optical tweezer relative to the auxiliary object, a pushing force or a pulling force of the optical tweezer on the auxiliary object being transferred onto the target cell by the adhered auxiliary object resulting in said deformation." Support for the amendment is as discussed with respect to claim 16.

New claim 34 adds an analyzing action to the method of claim 16. The dependent claim recites "determining a visco-elastic property of the target cell by analyzing said deformation." Support for the amendment is found in the passages below and elsewhere in the specification.

"The mechanical deformation of cells can be used to determine visco-elastic parameters. As a couple of dynamic processes (growth, adhesion to substrate, migration, phagocytosis) are linked with a changed cellular visco-elasticity, valuable conclusions can be drawn from the

mechanical properties of a cell regarding multiple vital parameters" (page 1, lines 20-26). "As important information on the structure of the cytoskeleton and of the cortical actin in particular can be gained from the determination of visco-elastic properties, the method is of great practical importance in the research and diagnosis of diseases which are linked to abnormalities of the cytoskeleton" (page 10, lines 27-32). "The optically induced forces are the reason for the erythrocyte to be pulled towards the focus. That way the erythrocyte pushes onto the cell and deforms the latter within this area. The deformation of cell is measured via an optical recording and image analysis..." (page 12, lines 20-25). Thus, analysis of the deformation of the target cell is used to determine a visco-elastic property of the target cell, as disclosed in the specification.

New claim 35 adds an action of determining whether an event has occurred on the target cell resulting from practicing the method of claim 16. The dependent claim recites "determining an activation of a mechano-sensitive ion channel of the target cell resulting from said deformation." Support for the amendment is found in the passage below and elsewhere in the specification.

"This invention enables the deformation of adherent cells for several micrometers. Furthermore, it is possible to activate mechano-sensitive ion channels as proved by a very prominent increase of intracellular calcium following the deformation by the laser. These experiments were conducted successfully using different cell types..." (page 9, line 29-page 10, line 2). Thus, the deformation of a target cell, using the method of claim 16, resulted in activation of a mechano-sensitive ion channel of the target cell in successful experiments as disclosed in the specification.

Claim Rejections under 35 USC §103(a)

Claims 16, 19, 21, 24, 25, 26, 28, 30, and 32 are rejected under 35 USC §103(a) as being made obvious by Kas et al. (US 6,067,859) hereinafter Kas, in view of Stromberg et al. (PNAS, 2000, Vol. 97, p.7-11) hereinafter Stromberg. Claims of 17 and 18 are rejected under 35 USC §103(a) as being made obvious by Kas et al. (US 6,067,859), in view of Stromberg et al. (PNAS, 2000, Vol. 97, p.7-11) and further in view of Nishiguchi et al. (Cell Structure and Function, 1998, Vol. 23, p.143-152) hereinafter Nishiguchi. Claims 29, 31 and 33 are rejected under 35 USC §103(a) as being made obvious by Kas et al. (US 6,067,859), in view of Stromberg et al. (PNAS, 2000, Vol. 97, p.7-11), in view of Nishiguchi et al. (Cell Structure and Function, 1998, Vol. 23, p.143-152) and further in view of Endlich (2001; IDS filed 5/21/2004) hereinafter Endlich.

Independent Claims 16 and 21

In making the rejection, the Office Action asserts that Kas teaches an improved optical tweezer system, Stromberg teaches optically trapping fused cells, and that it would have been obvious to modify the method of Kas combined with the teachings of Stromberg to produce the limitations of claim 16 and 21. The stated motivation for adhering cells in combining the references would have been to move the cells to different locations on a surface, as shown by Stromberg, or to perform genetic identity experiments by creating specific fusion products, as shown by Stromberg. Applicant respectfully disagrees with the rejection and has amended claims 16 and 21 to clarify the claimed method and system, thus further distinguishing from the references.

Obviousness and Reason or Suggestion in the Art

On the subject of obviousness and rejections under 35 USC §103, the following cases are relevant.

> In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991):
>
> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under §103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success... both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure.

> In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988):
>
> Obvious to experiment" is not a proper standard for obviousness; "[S]elective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure.

Cited References Do Not Teach Claimed Elements

Applicant acknowledges that Kas includes a teaching of an improved optical tweezer in a background reference to the "Optical Tweezers and Spanners" of M. Padget and L. Allen (see column 3 paragraph 4 and column 4 paragraph 1), and that Stromberg references an optical tweezer (see page 3 column 1 paragraph 4 and column 2 paragraph 1) and teaches fusion of cells.

The "Optical Stretcher" of Kas (see title and elsewhere in the reference) is a type of optical trap but is not a type of optical tweezer. The optical stretcher applies radiation pressure of two opposing laser beams to stretch a cell, making use of momentum conservation of the laser beam and a compensating pulling force (see column 6, lines 49-67 and column 7, lines 13-19), a mechanism which differs from that of the optical tweezer. Optical tweezers rely on gradient forces near the focus of a laser beam (see column 1 lines 43-51 and column 2 lines 8-24) while the optical stretcher relies on a diverging beam (see column 17, lines 51-55). Individual cells are trapped and stretched by the optical stretcher.

Kas is silent as to adhering an auxiliary object to a target cell, inducing mechanical forces on the target cell by application of any sort of optical trap to such an auxiliary object, and directing a mechanical deformation of the target cell by using optical tweezers or any sort of optical trap relative to the auxiliary object, as in claim 16. The reference is silent as to selecting such an auxiliary object from a group consisting of erythrocytes, haemoglobin, a haemoglobin derivate, a chromophore and a chloroplast. Selection of such an auxiliary object from the claimed group is disclosed by Applicant, based on experiments performed and described, and is not found in the reference. The reference is silent as to applying an optical tweezer to such an auxiliary object. The reference is silent as to a pushing force or a pulling force of an optical tweezer on such an auxiliary object being transferred onto a target cell by the adhered auxiliary object. Such actions and mechanisms are described by Applicant, based on experiments performed, and are not found in the reference.

Stromberg, while referencing optical tweezers, prefers to use carbon-fiber microelectrode tips (CFE or carbon-fiber electrodes) to place cells or vesicles on a glass surface next to a target cell (see Figs. 1-4, page 3 column 1 paragraph 2 and page 3 column 2 paragraph 2). Stromberg, too, is silent as to the above-discussed limitations of claim 16.

Mechanical deformation of a target cell occurs in a broad sense in Stromberg, as a result of cells being moved with carbon-fiber electrodes and having a flattened contact zone after dielectrophoresis (see Fig. 2). However, such broadly realized deformation of a target cell in Stromberg is a result of initial cell to cell contact and subsequent biological processes and is not directed by using an optical tweezer and an auxiliary object in the claimed manner, and no suggestions are contained in the references for exploring such directed deformation as claimed. The asserted motivation for attaching cells, to move them to different locations on a surface or to perform genetic identity experiments by creating specific fusion products, does not render obvious the claimed directed mechanical deformation of a target cell, the use of the claimed auxiliary object in the claimed manner to direct the deformation of the target cell or the selection of the auxiliary object from the claimed group.

As discussed above, the claimed subject matter is found in the disclosure of Applicant, and not in the references. The references do not provide a suggestion of how to select an auxiliary object, from what group such an auxiliary object should be selected or a reasonable expectation of success if an auxiliary object is selected having the claimed limitations. The references do not provide a suggestion of using the auxiliary object in the claimed manner. The references do not teach a directed deformation of a target cell in the claimed manner. For at least these reasons, claim 16 is nonobvious over the references.

The above reasons apply further to independent claim 21.

No Teaching to Combine References

MPEP §2143(A) (Example 1:) recites:

> "When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious." *KSR*, 550

U.S. at ___, 82 USPQ2d at 1395.

MPEP §2145(X)(D.)(3.) recites:

> 3. Proceeding Contrary to Accepted Wisdom Is Evidence of Nonobviousness
>
> The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986) (Applicant's claimed process for sulfonating diphenyl sulfone at a temperature above 127°C was contrary to accepted wisdom because the prior art as a whole suggested using lower temperatures for optimum results as evidenced by charring, decomposition, or reduced yields at higher temperatures.).
>
> Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams,* 383 U.S. 39, 52, 148 USPQ 479, 484 (1966).

Under patent law, the cited references much teach every claimed element and there must be some reason to combine the cited references. If the references teach away from combination this is a powerful reason to not combine the references and to find the claims not obvious. Kas recites, on the subject of optical traps, "Although these traps are extremely useful for all kinds of manipulations of objects, they can only translocate and/or rotate them and are *not intended to deform them.* The Optical Stretcher of this invention expands the line of optical tools and allows for a fill (sic) spectrum of particle manipulation" (column 4, lines 10-15, emphasis added). In the SUMMARY OF INVENTION, Kas recites "There exist several optical tools for the manipulation of dielectric particles such as biological cells. Until now, manipulation by radiation pressure was considered to be translation and rotation. This is the first time that the forces arising from the interaction of light with matter are used

intentionally to deform cells in a controlled and nondestructive manner. With this novel tool, the "Optical Stretcher", it is possible to measure the elasticity of deformable objects, such as cells..." (column 4, line 65-column 5, line 6). In comparing the optical stretcher to other types of optical traps, Kas recites "Prior attempts to use light to deform (stretch) the cell led to destruction of the cell because the intensity of the beam was too strong" (column 8 lines 1-3).

Kas teaches that optical traps, with the exception of the Optical Stretcher, are not used to intentionally deform cells in a controlled and nondestructive manner. As discussed above with respect to claimed subject matter originating in the disclosure of Applicant, the Optical Stretcher is not an optical tweezer. Thus, the reference teaches away from using optical tweezers, or any known optical traps other than the optical stretcher, in a directed deformation of a target cell. A person skilled in the art and applying the teachings of the reference would be instructed to not use optical tweezers in a directed deformation of a target cell. Applicant respectfully asserts that discovery of a successful means of using the optical tweezers in a directed deformation of a target cell is contrary to accepted wisdom and nonobvious in light of the cited art teaching away from such use. For these reasons, claims 16 and 21 are nonobvious over the references and are allowable.

Dependent Claims

Although Nishiguchi discloses adhesion of red blood cells to each other, the reference is silent as to the above-discussed limitations of claims 16 and 21. Endlich discloses mechanical stress experiments on mouse podocytes. However, in Endlich, a large group of cells in a six-well plate is mechanically stressed by cyclic air pressure variations (see page 2, column 1 paragraph 5), and the reference is silent as to the above-

discussed limitations of claims 16 and 21. Thus, the independent claims are nonobvious over the cited references. As the dependent claims depend from and further limit allowable independent claims, claims 17-19, 24-26 and 28-35 are allowable.

New Dependent Claims

Added dependent claim 34 recites "determining a visco-elastic property of the target cell by analyzing said deformation." As discussed with respect to claim amendments, such action is disclosed in the specification. The references are silent as to such action using the claimed method. Thus, claim 34 is nonobvious over the references. Further, since claim 34 depends from and further limits allowable independent claim 16, claim 34 is allowable.

Added dependent claim 35 recites "determining an activation of a mechano-sensitive ion channel of the target cell resulting from said deformation." As discussed with respect to claim amendments, such action is disclosed in the specification. The references are silent as to such action using the claimed method. Thus, claim 35 is nonobvious over the references. Further, since claim 35 depends from and further limits allowable independent claim 16, claim 35 is allowable.

Conclusion

Independent claims 16 and 21 are amended and respectfully asserted to be nonobvious and allowable. The dependent claims, including new claims 34 and 35, are respectfully asserted to be nonobvious and allowable. Applicant requests Reconsideration and a Notice of Allowance.

The Examiner is invited to contact the undersigned with any comments or questions at 408-297-9733 between 9:00 AM and 5:00 PM PST.

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CERTIFICATE OF TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) on the date shown below.

Signed: Sally Azevedo
Typed Name: Sally Azevedo

Date: June 28, 2010

Respectfully submitted,

Christopher M. Hall

Christopher M. Hall
Reg. No. 62,908

Schneck & Schneck
P.O. Box 2-E
San Jose, CA 95109-0005
(408) 297-9733